PRIMARY DISEASES OF MYELIN

By: Shifaa’ Al Qa’qa’

in this lecture we'll talk about myelin diseases in the CNS & PNS
• Most diseases of myelin are primarily white matter disorders???

Myelinated axons

as we know: the white matter contains axons of neurons, many of them are surrounded by myelin sheath, and myelinated axons are more abundant in white matter that's why diseases of myelin occur primarily in white matter
• most diseases of CNS myelin do not involve the peripheral nerves to any significant extent, and vice versa. ?????

myelin in the CNS is produced by oligodendrocytes while it is produced by schwann cells in the PNS which makes its composition (lipids, proteins) and structure different
In general, diseases involving myelin are separated into two broad groups:

- **Demyelinating diseases** of the CNS:
  - Acquired
  - Damage to previously normal myelin
  - E.g:
    - Multiple sclerosis (MS)--- immune immune-mediated injury
    - progressive multifocal leukoencephalopathy---- viral

- **Dysmyelinating diseases** (leukodystrophy):
  - Inherited
  - myelin is not formed properly or has abnormal turnover kinetics
Multiple Sclerosis

• Autoimmune demyelinating disorder

• Characterized by distinct episodes of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space
• the most common of the demyelinating disorders,

• become clinically apparent at any age, although onset in childhood or after age 50 is relatively rare.

  * common in young to middle age
  * common in young females
  * women:men =2:1

• Women are affected twice as often as men.
• In most patients with MS, the illness shows relapsing and remitting episodes of neurologic impairment.
  *unpredictable attacks or episodes
  *attacks vary in frequency from a patient to another
  some patients may face a single attack while others may face multiple, recurrent attacks for a short period of time or others for a long period

• The frequency of relapses tends to decrease during the course of the illness, but a steady neurologic deterioration is characteristic in a subset of patients.
PATHOGENESIS: is not completely understood

Environmental and genetic factors that result in a loss of tolerance to self proteins (myelin antigens).

initiating agent??? Infectious?????

viral infections of any kind (common cold, gastroenteritis, .....)

----> loss of self tolerance

genetic factors:

- first-degree relative, father, mother, sister, brother
- monozygotic twins, > dizygotic
- HLA-DR variants,
- polymorphisms of cytokines IL-2 and IL-7 receptor gene (regulation of T cell)

All of these genetic factors increase susceptibility to MS
immune-mediated myelin destruction is thought to have a central role in MS

A central role for CD4+ T cells has been suggested, with an increase in TH17 and TH1 CD4+ cells thought to be a critical component of the injury to myelin.

There is also evidence for important contributions from CD8+ T cells and B cells.
• MS is characterized by the presence of demyelination out of proportion to axonal loss, some injury to axons does occur.

  the disease primarily affects myelin sheath but secondary axonal damage may occur

• Toxic effects of lymphocytes, macrophages, and their secreted molecules have been implicated in initiating the process of axonal injury, sometimes even leading to neuronal death.
• experimental allergic encephalomyelitis?

experiencing on animals
(MS) model in animals

how ??
injecting experimental animals with a thing that
provokes the immune system and causes loss of
self-tolerance similar to what happens in MS
changes in CNS : Gross or microscopic

• MORPHOLOGY: white matter disease

Plaques: gross changes

- multiple, well-circumscribed, slightly depressed, glassy-appearing, gray-tan, irregularly shaped lesions.

- commonly arise near the ventricles.

- frequent in the optic nerves and chiasm, brain stem, ascending and descending fiber tracts, cerebellum, and spinal cord.

plaques can be seen after performing an autopsy on a dead patient or using MRI on an alive one
*those are plaques not hemorrhages
*what are plaques? areas of demyelination determined microscopically by the presence of macrophages
Demyelinated areas can't be recognized using H&E stain which only shows abundant macrophages, so a special stain is used (LUXOL FAST BLUE).

Where areas of myelin appear in blue.

And areas of demyelination appear pale.
- Sharply defined borders at the microscopic level.
- chronic inflammatory cells
2 types of plaques: active and inactive plaques

• **active plaque:**
  - abundant macrophages containing myelin debris (ongoing myelin breakdown),
  - Lymphocytes and macrophages are present, mostly as perivascular cuffs, around blood vessels
  - Axons are relatively preserved but may be reduced in number.

  axons are either normal or secondarily injured (reduced in number)
Active plaques fall into four classes:

- **Type I**: The recognized microscopic patterns are, which has macrophage infiltrates with sharp margins.

- **Type II**: similar to type I but also shows complement deposition (antibody-mediated component).

- **Type III**: with less well-defined borders and oligodendrocyte apoptosis.

- **Type IV**: with nonapoptotic oligodendrocyte loss.
inactive plaques:
- Quiescent plaques,
- the inflammation mostly disappears, leaving behind little to no myelin.
- astrocytic proliferation and gliosis are prominent.

the only determinant is LUXOL FAST BLUE special stain because there are no macrophages or lymphocytes
• Clinical Features:
  - The course of MS is variable
  - Multiple relapses followed by episodes of remission
  - over time there is usually a gradual, often stepwise, accumulation of neurologic deficits
the most common symptom is optic neuritis (when MS involves the optic nerve) causing loss of vision in one eye if a patient had optic neuritis without MS, developing MS is definite in a while!!

the 2nd most common symptom is depression in the form of attacks

the disease differs in severity from a patient to another one might end up bedridden while the other faces a single attack during his life
The CSF in patients with MS:

- **Mildly elevated protein level**
- **increased proportion of immunoglobulin**;
  **oligoclonal bands** --- markers of disease activity
- **moderate pleocytosis**

Lymphocytic pleocytosis

In normal CSF there are uniform bands while in MS there are oligoclonal bands (1 type if immunoglobulin causing multiple bands)
Other Acquired Demyelinating Diseases

- Acute disseminated encephalomyelitis
- Acute necrotizing hemorrhagic encephalomyelitis:
  - postinfectious autoimmune reactions to myelin
  - unlike in MS, they are associated with acute-onset monophasic illnesses
  - symptoms typically develop a week or two after an antecedent infection and are nonlocalizing (headache, lethargy, and coma), in contrast with the focal findings of MS.
  - fatal in as many as 20% of cases

**after viral or bacterial infection
**in children it can be seen after vaccination especially with measles vaccine
Neuromyelitis optica (NMO): known as DEVIC'S disease

- inflammatory demyelinating disease centered on the optic nerves and spinal cord
- This is now recognized to be an antibody-mediated autoimmune disorder. Antibodies to the water channel aquaporin-4 are both diagnostic and pathogenic.
Central pontine myelinolysis:
- nonimmune process.  correction of electrolyte disturbance must be gradual
- loss of myelin involving the center of the pons, most often after rapid correction of hyponatremia.
- The mechanism of oligodendroglial cell injury is uncertain, but it may be related to edema induced by sudden changes in osmotic pressure.
- Because of the involvement of fibers in the pons carrying signals to motor neurons in the spinal cord, patients often present with rapidly evolving quadriplegia.
mentioned previously in this lecture

• progressive multifocal leukoencephalopathy (PML)
Leukodystrophies

- inherited dysmyelinating diseases in which the clinical symptoms derive from abnormal myelin synthesis or turnover.
  - Mutation in genes responsible or contribute in myelin synthesis:
  - Lysosomal enzymes, peroxisomal enzymes; a few are associated with mutations in myelin proteins.
- Most are of autosomal recessive inheritance, although X-linked diseases also occur.
<table>
<thead>
<tr>
<th>Metabolic Disorder</th>
<th>Inheritance Mode</th>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>AR</td>
<td>Arylsulfatase A deficiency</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>AR</td>
<td>Galactocerebroside β-galactosidase deficiency</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>AR, X</td>
<td>Peroxisomal defects; elevated very-long-chain fatty acids</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>AR</td>
<td>Aspartoacylase deficiency</td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher disease</td>
<td>X</td>
<td>Mutations in proteolipid protein</td>
</tr>
<tr>
<td>Vanishing white matter disease</td>
<td>AR</td>
<td>Translation initiation factor; link to myelin unclear</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>AR</td>
<td>Mutations in glial fibrillary acidic protein</td>
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</tbody>
</table>

AR, autosomal recessive; X, X-linked.
• **white matter**, which is diffusely abnormal in color (gray and translucent) and volume (decreased).

• With the loss of white matter, the **brain** becomes **atrophic**, the **ventricles enlarge**

• Myelin loss leads to infiltration of **macrophages**,.
• Affected children are normal at birth but begin to miss developmental milestones during infancy and childhood.

• Diffuse involvement of white matter leads to deterioration in motor skills, spasticity, hypotonia, or ataxia. In general, the earlier the age at onset, the more severe the deficiency and clinical course.
Patterns of Peripheral Nerve Injury

• Most peripheral neuropathies can be subclassified as either axonal or demyelinating, even though some diseases exhibit mixed features.
**Axonal neuropathies:** primarily from trauma or axonal entrapment

- Axonal degeneration is associated with secondary myelin loss---**Wallerian degeneration**---The entire distal portion of an affected axon degenerates ---- Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon
• **Demyelinating neuropathies:**
  - Damage to Schwann cells or myelin with relative axonal sparing, resulting in abnormally slow nerve conduction velocities.
  - Segmental demyelination: occurs in individual myelin internodes randomly
Axonal injury due to cut in nerve --> Wallerian degeneration

***Muscles supplied by this nerve become atrophic but after regeneration the muscle becomes normal again.

Axon is normal, damage in internodes (myelin sheath around nerves) --> segmental

After regeneration takes place axons regrow and remyelination occurs but the myelin sheath looks thin and internodes look shorter than normal.
Peripheral neuropathies:

1. Polyneuropathies—symmetric, length-dependent fashion, distal segments
2. Polyneuritis multiplex—damage randomly
3. Simple mononeuropathy—single nerve, carpal tunnel syndrome can be:
   - Motor
   - Sensory
   - Mixed

- Diabetes is the most common cause of peripheral neuropathy.
stocking and glove distribution of nerve injury
parathesia or numbness starts in feet, ascends to ankles, knees and might reach the hands
<table>
<thead>
<tr>
<th>Etiologic Category</th>
<th>Causative Disorders/Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional and metabolic</td>
<td>Diabetes mellitus, Uremia, Vitamin deficiencies—thiamine, vitamin B_6, vitamin B_12</td>
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<td>Toxic, Drugs, including vinblastine, vincristine, paclitaxel, colchicine, and isoniazid</td>
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<td></td>
<td>Other toxins—alcohol, lead, aluminum, arsenic, mercury, acrylamide</td>
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<tr>
<td>Vasculopathic</td>
<td>Vasculitis</td>
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<td></td>
<td>Amyloidosis</td>
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<tr>
<td>Inflammatory</td>
<td>Autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis,</td>
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<td></td>
<td>Sjögren syndrome, Guillain-Barré syndrome</td>
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<td></td>
<td>Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
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<tr>
<td>Infections</td>
<td>Herpes zoster—most often ganglionitis</td>
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<td></td>
<td>Leprosy</td>
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<td></td>
<td>HIV infection</td>
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<td></td>
<td>Lyme disease—often facial nerve palsy</td>
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<tr>
<td>Inherited</td>
<td>Charcot-Marie-Tooth neuropathy, type 1: autosomal dominant (many cases with tandem</td>
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<td></td>
<td>duplications in PMP22</td>
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<tr>
<td></td>
<td>Charcot-Marie-Tooth neuropathy, type 3: autosomal dominant or recessive (some with</td>
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<tr>
<td></td>
<td>point mutations in PMP22</td>
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<tr>
<td></td>
<td>Charcot-Marie-Tooth neuropathy, X-linked (connexin 32 gene mutations)</td>
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<tr>
<td></td>
<td>Hereditary neuropathy with liability to pressure palsy: autosomal dominant deletions of</td>
</tr>
<tr>
<td></td>
<td>PMP22</td>
</tr>
<tr>
<td>Others</td>
<td>Paraneoplastic, some leukodystrophies</td>
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</table>
Guillain-Barré Syndrome

- Is one of the most common lifethreatening diseases of the peripheral nervous system.

- It is a rapidly progressive acute demyelinating disorder affecting motor axons that results in ascending weakness that may lead to death from failure of respiratory muscles over a period of only several days.
affects children when a child becomes infected with gastroenteritis or any other infection mainly by CAMPYLOBACTER JEJUNI cross linking between bacterial antigen and myelin sheath around peripheral nerves --> autoimmune reaction attacks myelin --> demyelination

• appears to be triggered by an infection or a vaccine that breaks down self-tolerance ---- autoimmune response.

• Both humoral and cellular immune responses are believed to play a role in the disease process

• infectious agents include Campylobacter jejuni, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus
Treatments include:
- plasmapheresis (to remove offending antibodies),
- intravenous immunoglobulin infusions (which suppress immune responses through unclear mechanisms)
- supportive care, such as ventilatory support.

Patients who survive the initial acute phase of the disease usually recover over time.
DISORDERS OF NEUROMUSCULAR JUNCTION

targets different areas

• Myasthenia Gravis
• Lambert-Eaton Syndrome
Myasthenia Gravis

- is caused by autoantibodies that block the function of postsynaptic acetylcholine receptors at motor end plates, which results in the degradation and depletion of the receptors.

- like many autoimmune disorders, is more common in females

- 60% of cases are associated with a peculiar reactive hyperplasia of intrathymic B cells (often referred to as thymic hyperplasia),
- another 20% are associated with thymoma, a tumor of thymic epithelial cells—generation of autoreactive T and B cells.
Clinically, myasthenia gravis frequently manifests with ptosis (drooping eyelids) or diplopia (double vision) due to weakness in the extraocular muscles.

This pattern of weakness is distinctly different from that in most primary myopathic processes, in which there is relative sparing of facial and extraocular muscles.
Characteristically, repetitive use or electrophysiologic stimulation of muscles makes the weakness more severe,

whereas administration of cholinesterase inhibitors improves strength markedly;

both of these features are diagnostically useful.
Effective treatments include:
- cholinesterase inhibitory drugs,
- immunosuppression,
- plasmapheresis,
- and (in patients with thymic lesions) thymectomy.
differs from pure myopathy that it affects facial and ocular nerve leading to paralysis in extraocular or facial muscles.
Lambert-Eaton Syndrome

a paraneoplastic syndrome
bad prognosis associated with lung carcinoma

• is caused by autoantibodies that inhibit the function of **presynaptic calcium channels**, which reduces the release of acetylcholine into the synaptic cleft.

• In contrast with those suffering from myasthenia gravis, patients with Lambert-Eaton syndrome experience improvement in weakness with repetitive stimulation. This serves to build up sufficient intracellular calcium to facilitate acetylcholine release.
Like myasthenia gravis, however, the disorder can be transferred to animals through the serum of affected patients.

often arises as a paraneoplastic disorder--small cell lung carcinoma

Cholinesterase inhibitors are not effective,

Therapy: plasmapheresis or immunosuppression.

Owing to the strong link to lung cancer, the overall prognosis for patients with Lambert-Eaton syndrome is substantially worse than for those affected by myasthenia gravis.

BEST OF LUCK ^^